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t(14;16)(q32;q23) IGH/MAF

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Abstract

Review on t(14;16)(q32;q23) IGH/MAF, with data on clinics, and the genes involved.

Keywords

Chromosome 14; Chromosome 16; IGH; MAF; Multiple myeloma; Plasma cell leukemia

Identity

Note

t(14;16)(q32;q23) represents 14q32/IGH rearrangement and belongs to the group of IGH/MAF translocations (rearrangements of the genes from the MAF oncogene family MAF, MAFA and MAFB with the IGH locus). As the other two IGH/MAF translocations t(8;14)q24;q32) andt(14;20)(q13;32) is described only in plasma cell neoplasms (PCN). t(14;16)(q32;q23) resulted in the juxtaposition of the oncogene MAF (located at 16q23) to the strong enhancer of the IGH gene (located at 14q32) causing its up regulation in the plasma cells. This anomaly is found in both multiple myeloma (MM) and its precursor monoclonal gammapathy of undetermined significance (MGUS) respectively in 5% (Avet-Loiseau et al, 2007; Fonseca et al, 2009) and 1-5% (Avet-Loiseau et al, 2002; Fonseca et al, 2002) of the cases with 14q32 rearrangements . The anomaly is cryptic and therefore in the routine practice is determinated by fluorescent in situ hybridization with DNA specific probes and/or by qPCR technique. It is difficult to be proved with the classical G-banding technique and because of this only a small number of cases with karyotypic description of t(14;16) have been reported.

Clinics and pathology

Disease

Multiple myeloma (MM)

Phenotype/cell stem origin

t(14;16) is generated during B-cell maturation in germinal centers possibly as a result of errors in the IGH switch recombination (Bergsagel et al, 2001). The anomaly appears to be an early event in the genesis of plasma cell neoplasms (PCN) as it occurs in both MGUS and MM.

Epidemiology

t(14;16) is described in 12 cases (Mitelman database) (0.6% of all MM cases with abnormal karyotypes) (Gabrea et al, 2008; Le Baccon et al, 2001; Lioveras et al, et al, 2004; Mohamed et al, 2007; Rack et al, 2016; Sawyer et al, 1998; Sawyer et al, 2014; Smadja et al, 2003). Examinations of the large series with MM (cytogenetic diagnosis included IGH-MAF fusion probe) showed that the frequency of t(14;16) is very low - 2.2-3.2% of all MM cases (Avet-Loiseau et al, 2010; Pavlistova et al, 2017; Mickova et al, 2013). The sex ratio is M:F=1.4:1 and the anomaly has been observed only in older patients (4 cases documented: average age 62 years; range 55-72 years). The presented median age is in agreement with the data of the median patients age of the largest series with t(14;16) positive MM cases (32) reported by Avet-Loiseau et al, 2010 (63 years; range 45-75 years).

Clinics

It has been suggested that t(14;16) positive MM cases are associated with less frequent extramedullary tumor formation and negativity for

CD56 expression. In the cases with t(14;16) is found also higher frequency of the IgG subtype M protein, leukocytosis, thrombocytemia, hypercalcemia and lower frequency of hypocalcemia compared with those without t(14;16) (Narita et al, 2015). The cases with t(14;16) are resistant to bortezomib therapy, because proteasome inhibitors abrogate glycogen synthase kinase 3 beta - mediated degradation of MAF protein leading to its stabilization (Qiang et al, 2016)

Cytogenetics

All reported cases presented in Mitelman database except one (with isolated t(14;16)) are with complex karyotypes. Two of them are with hyper-diploid, two with pseudo-diploid and six with hypo-diploid karyotypes. The cases with hyper-diploid karyotypes included trisomy of chromosome 3, 9, 15, 18, 19, 20 and 21 and the cases with hypo-diploid karyotypes the loss of chromosome 4, 11, 13, 16,-18, 20 and 22. All cases with complex karyotypes are associated with structural abnormalities of chromosome 1 and all except one with abnormalities of chromosome 13. Chromosome 1 anomalies are presented predominantly with unbalanced translocations including whole arm translocations with the partner chromosomes 4, 5, 8, 15, 16, 18, 19, 20 and 22. In most of the cases the breakpoint in chromosome 1 is in the region 1q10-21. Four cases have deletions of the short arm of chromosome 1 in the region 1p11-33 and in two cases additional material of unknown origin is attached to the bands 1q21 and 1p22. The abnormalities of chromosome 13 included monosomy of chromosome 13 in six cases and 13q deletions (in the region 13q12-22) in three cases. Deletions of 17p12 is found in two cases and numerical anomalies of the sex chromosomes in four cases (three cases with -Y and one with -X). The presented information of the additional anomalies are partially in agreement with the findings of the large cytogenetic series with MM carrying t(14;16). The most common additional abnormalities in these series are -13/13q-, amplification of 1q, trisomy or tetrasomy of chromosome 15 and structural (mostly deletions of the short arm in the region 8p21.3) and numerical of chromosome 8. Coincidence of both anomalies t(4;14) and t(14;16) is not observed (Avet-Loiseau et al, 2010; Kadam Amere et al, 2016; Mickova et al, 2013).

Disease

Plasma cell leukemia

Epidemiology

Two cases are reported (53 and 55 years old males) (Avet-Loiseau et al., 2001; Stella et al, 2011).

Cytogenetics

Both cases showed complex karyotypes: one with hyperdiploid and numerical anomalies (+8, +9, +18 and -13) and the other with hypodiploid karyotype and numerical (-Y, -7, -8, -13, -14 and +21) and structural anomalies, including 1q rearrangements.

Prognosis

There is controversy about the prognostic value of t(14;16). Negative impact on prognosis has been suggested by Fonseca et al., 2003 and Nair et al, 2010. Pavlistova et al, 2017 identified that the median overall survival (OS) was shorter in comparison with the control group, but was not statistically significant. Avet-Loiseau et al, 2010 reported that by univariate analysis t(14;16) is not prognostic to age, beta2-microglobulin level, t(4;14), del(17p) and del(13q) and in multivariate analysis, the p value associated with t(14;16) is even less significant. The authors also found no difference for OS. Because of the contradictory data larger number of cases carrying t(14;16) is needed to establish the real prognostic relevance of t(14;16).

Genetics

Note

The predisposing factors leading to the appearance of the myeloma associated 14q32 rearrangements including t(14;16) are still unknown. The formation of the 14q32 rearrangements requires nuclear co-localization of the IGH with the partner genes involved in the 14q32 translocations, respectively in the case of t(14;16) - nuclear co-localization of IGH with MAF. But the 3D FISH experiments provided by Martin et al, 2013 indicated that the MAF and IGH are not co-localized in the nucleus of the non-malignant B cells. In these cells MAF is located more peripherally in the nucleus while IGH occupies more central nuclear position. Obviously, in order for MAF to reach the nuclear position of IGH, large chromatin decondensation in the region of its locus is necessary to occur. The latter could be a consequence of an ectopic expression of the MAF gene. As is noted below, MAF is activated by ERK/MEK pathway probably as a result of RAS or BRAF mutations but these mutations are late event in MM. One possible activator of MAF in the stage of B-cell maturation in germinal centers could be the small MAF protein BATF. This transcription factor is responsible for the differentiation of the follicular T-helper cells controlling the expression of both BCL6 and MAF. In B-cells BATF is involved in class-switch recombination (CSR) controlling directly the expression of both activation-induced cytidine deaminase and I_H-C_H germline transcripts (Ise et al, 2011). It has been shown also that BATF induced high level of the T-bet expression through chromatin remodelling promoting effector differentiation and cell survival (Kuroda et al, 2011). However, one possible BATF induced activation of MAF required additional chromatin deregulation of

the MAF locus (to be achieved open chromatin structure), because MAF is silent in mature B-cells. But if an ectopic MAF expression is occurred during an ineffective CSR (existence of unrepaired double-strand DNA breaks in the switch regions of IGH) would be at high risk for the appearance of t(14;16).

Genes involved and proteins

IGH

Location
14q32.33

MAF

Location
16q23.2

Note
MAF is a member of the basic leucine zipper transcription factors belonging to the AP1 superfamily that includes the JUN, FOS, ATF, CREB and MAF family. MAF encodes two protein isoforms which differ in their carboxy-terminus - MAF short and long form (have 30 extra amino-acids). As the other large Maf proteins (MAFA,-MAF, MAFB and NRL), MAF contains the b-Zip domain, as well as an additional amino-terminal transactivation domain (Eychene & Pouponnot, 2009-11). MAF gene plays a role in the embryonic lens fiber cell development and its germinal mutation is responsible for congenital cataract in humans. The MAF target genes are CCND2 (cyclin D2), ITGB7 (integrin beta7) and CCR1 (C-C chemokin receptor 1). All three genes are up-regulated by MAF protein and have an important role in MM for the cell cycle progression (cyclin D2) and adhesion of the myeloma cells to bone marrow stroma cells (integrin beta 7 and CCR1) (Hurt et al, 2004). Additionally, in MM cases integrin beta 7 binds to CDH1 (E-cadherin) on the surface of stroma cells and increases the production of VEGFA (vascular endothelial growth factor) which resulted in enhanced bone marrow angiogenesis and autocrine and paracrine stimulation of the myeloma cells (Podar et al, 2001; 2002). MAF is expressed in many tissues including neural tissues, small intestine, skin and kidney. In the normal hematopoietic tissue MAF is expressed only in the nuclei of T helper 2 (TH2) cells, monocytes and macrophages, controlling the expression of IL4 and IL10 (interleukin 4 and 10) (Cao et al, 2005; Kim et al, 1999), while in the plasmocytes MAF mRNA is not expressed (Natkunam et al, 2009). It has been reported that MAF is up-regulated in B, T, NK-cell neoplasms, myeloma cell lines and approximately in 50% of the MM cases lacking t(14;16) translocation (Hurt et al, 2004; Natkunam et al, 2009).

Based on the finding that the inhibition of the MEK-ERK pathway reduced the MAF transcription in cell lines and MM cases with MAF overexpression, Annunziata et al, 2011 proposed that the MAF up regulation in MM cases lacking t(14;16) is possibly caused by the activation of MEK-ERK signalling cascade.
The latter is in agreement with the observation that MAF is overexpressed in the hairy cell leukemia (HCL) (Natkunam et al, 2009) where the causal genetic event is the BRAF-V600E mutation (Arcaini et al 2012). As in HCL in MM aberrant MEK-ERK pathway is also found. Mutations of KRAS, NRAS and BRAF are detected in up to 50% of the newly diagnosed MM patients, but it has been shown that only KRASG12D and BRAFV600E are consistently associated with ERK activation (Xu et al, 2017). It is logical to expect that in MM with these two mutations MAF will be overexpressed.

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